Cle disorder, anxiety, depression, mild cognitive impairment, dyslexia, schizophrenia and Tourette's syndrome.

Remarks

Claims 1-16, 22-41, 48-66 and 73-75 are pending. Claims 1, 16, 25, 41, 51 and 66 have been amended for clarity as suggested by the Examiner. Claims 51 and 66 have been amended to specifically list the CNS disorders to be treated, as requested by the Examiner. None of the amendments presents new matter. The Examiner is respectfully requested to enter the amendments.

Interview with the Examiner

Applicants wish to thank the Examiner for the helpful interview held on March 5, 2003. In the interview, the Examiner indicated that the proposed claim amendment (stating that Z'"j referred to j number of Z'" substituents) would overcome the enablement rejection. Further, the Examiner indicated that method claims would be allowable for those indications where the literature supported the use of nicotinic compounds for treating the disorder. The Examiner suggested amending the claims to include the list of disorders from the specification, and providing literature support for the use of nicotinic compounds to treat each listed disorder, which Applicants have done.

Rejections under 35 U.S.C. 112, Second Paragraph

Claims 1-16, 22-41, 48-66 and 73-75 have been rejected under 35 U.S.C. 112, second paragraph, as indefinite. Applicants respectfully traverse the rejections as applied to the amended claims.

The Office Action suggested that the term -- Z'''_j --was indefinite. This term is intended to encompass the presence of j number of Z'" substituents. To clarify this, Applicants have amended the claims to recite that Z'''_j refers to j number of Z'" substituents. Accordingly, the rejection should be withdrawn in light of the amendments to the claims.

Rejections under 35 U.S.C. 112, First Paragraph

Claims 52-66 and 73-75 have been rejected under 35 U.S.C. 112, first paragraph, as non-enabled. Applicants respectfully traverse the rejections as applied to the amended claims.

As a primary matter, these claims were rejected as obvious in view of PCT WO 99/32117 by Vernier, which teaches using purportedly similar compounds to treat substantially similar disorders. A proper obviousness rejection cannot be based on a non-enabling reference. Vernier, as well as the over forty references discussed in the Background of the Invention in the present application, teach that nicotinic compounds are useful for treating precisely the disorders described in the specification, and now specifically listed in the amended method claims.

During the interview with the Examiner, the Examiner indicated that if the claims were amended to list the specific CNS indications provided in the specification, and a paper teaching that nicotinic compounds are useful for treating each listed indication, the method claims would be allowable. Independent claims 51 and 66 have been amended as suggested by the Examiner to list specific CNS indications, including pre-senile dementia, Alzheimer's disease, HIV-dementia, multiple cerebral infarcts, Parkinsonism, Pick's disease, Huntington's chorea, tardive dyskindesia, hyperkinesias, mania, attention deficit disorder, anxiety, depression, mild cognitive impairment, dyslexia, schizophrenia and Tourette's syndrome. Support for the amendment is found on page 29, lines 24-30.

The Examiner has already stated that the Clementi reference teaches using nicotinic compounds for improving brain function in dementia and for treating smoking addiction. Clementi supports the fact that the claimed nicotinic compounds (though not disclosed or suggested by Clementi) are useful for treating dementia. As claimed, the compounds are used to treat pre-senile dementia, senile dementia, and HIV-dementia, each of which is supported by Clementi.

PCT WO 99/32117 by Vernier was cited by the Examiner under 35 U.S.C. 103 (a), and Applicants are entitled to a presumption that any art cited by the Examiner is enabling (i.e., an obviousness rejection cannot be based on non-enabling prior art). Vernier teaches that nicotinic compounds are useful for treating diseases of the central nervous system such as Alzheimer's disease and other diseases involving memory loss and/or dementia, including AIDS dementia (which also includes pre-senile dementia), cognitive dysfunction, including disorders of

attention, focus and concentration (which includes attention deficit disorder and dyslexia), Parkinson's disease, Huntington's disease (a.k.a. Huntington's chorea), Gilles de la Tourette syndrome, tardive dyskinesia, mood and emotional disorders such as depression, anxiety and psychosis (which includes schizophrenia), and substance abuse, including withdrawal symptoms and substitution therapy.

Accordingly, Vernier supports the fact that the claimed nicotinic compounds (though not disclosed or suggested by Vernier) are useful for treating Alzheimer's disease and other diseases involving memory loss and/or dementia (this includes Pick's disease, senile demential, pre-senile dementia, HIV-dementia), cognitive dysfunction, including disorders of attention, focus and concentration (which includes attention deficit disorder and dyslexia), Parkinson's disease, Huntington's disease (a.k.a. Huntington's chorea), Gilles de la Tourette syndrome, tardive dyskinesia, mood and emotional disorders such as depression, anxiety and psychosis (which includes schizophrenia), and substance abuse, including withdrawal symptoms and substitution therapy.

Additional references are discussed below in support of the claimed methods.

Blesa et al., "Galantamine provides sustained benefits in patients with 'advanced moderate' Alzheimer's disease for at least 12 months," *Dement. Geriatr. Cogn. Disord.* 15(2):79-87 (2003) (Abstract shown below)

> Galantamine (Reminyl), a novel agent with a dual mode of action, modulates nicotinic acetylcholine receptors and inhibits acetylcholinesterase. Galantamine has consistently demonstrated a broad range of beneficial effects and has shown sustained benefits in cognitive and functional abilities for at least 12 months in patients with mild-to-moderate Alzheimer's disease (AD). As pivotal studies demonstrating the efficacy of cholinergic drugs were designed to exclude patients with severer AD, many patients with the advanced stage of this condition are currently not treated due to the lack of demonstrated efficacy in clinical trials. We aimed to investigate whether there was any evidence for the benefits of galantamine in patients with severer disease, by performing a post hoc analysis using data extracted from the population of the two long-term galantamine studies. We evaluated the efficacy of galantamine in patients with 'advanced moderate' AD. 'Advanced moderate' patients were those with baseline Mini Mental State Examination (MMSE) scores </=14 or Alzheimer's Disease Assessment Scale - cognitive subscale (ADAS-cog) scores >30. These patients were compared with matched controls who received placebo in a different historical study. Cognitive abilities (assessed using

the ADAS-cog scale) of 'advanced moderate' AD patients receiving galantamine for 12 months were maintained at baseline levels after 12 months, and significantly improved over those of placebo patients ($p < 0.001$). Of the 'advanced moderate' patients receiving galantamine, 51% with baseline ADAS-cog of >30 maintained or improved their ADAS-cog scores over baseline values, compared with 13% receiving placebo ($p < 0.001$). In the subgroup of 'advanced moderate' patients with baseline MMSE </=14, 48% of those receiving galantamine and 4% of those receiving placebo maintained or improved their ADAS-cog scores at 12 months ($p = 0.001$). In both subgroups, the treatment difference (galantamine vs. historical placebo) amounted to approximately 10 points on the ADAS-cog scale. Functional abilities, as assessed using the Disability Assessment for Dementia scale, remained significantly superior in galantamine-treated patients compared with historical placebo-treated patients at 12 months ($p < 0.001$). In conclusion, galantamine offered sustained efficacy to patients with 'advanced moderate' AD, confirming the benefits seen in published studies of patients with mild-to-moderate AD. This drug has potential for broader use in clinical practice.

Woodruff-Pak et al., "Nicotinic cholinergic modulation: galantamine as a prototype," *CNS Drug Rev.* 8(4):405-26 (2002) (Abstract shown below)

Nicotinic acetylcholine receptor pharmacology is becoming increasingly important in the clinical symptomatology of neurodegenerative diseases in general and of cognitive and behavioral aspects in particular. In addition, the concept of allosteric modulation of nicotinic acetylcholine receptors has become a research focus for the development of therapeutic agents. In this review the scientific evidence for changes in nicotinic acetylcholine receptors in Alzheimer's disease is described. Within this context, the pharmacology of galantamine, a recently approved drug for cognition enhancement in Alzheimer's disease, is reviewed along with preclinical studies of its efficacy on learning and memory. Galantamine modestly inhibits acetylcholinesterase and has an allosteric potentiating ligand effect at nicotinic receptors. The data collected in this review suggest that the unique combination of acetylcholinesterase inhibition and nicotinic acetylcholine receptor modulation offers potentially significant benefits over acetylcholinesterase inhibition alone in facilitating acetylcholine neurotransmission.

Geerts et al., "Nicotinic receptor modulation: advantages for successful Alzheimer's disease therapy," *J. Neural. Transm. Suppl.* (62):203-16 (2002) (Abstract shown below)

Galantamine is a modest acetylcholinesterase inhibitor (AChEI) that is also an allosteric potentiating ligand (APL) of nicotinic acetylcholine receptors (nAChRs). In this report, these two effects are shown to be dependent upon each other using a realistic computer model of the cholinergic synaptic cleft. The model is based upon realistic estimates of the anatomy of a neuronal synapse, the kinetic states of pre- and postsynaptic nAChRs, and the acetylcholinesterase enzyme. The number of open postsynaptic nAChRs

per action potential is a measure of cholinergic neurotransmission. Using mathematical equations and published data, the effect of the AChEI and APL actions of galantamine is quantitatively described and compared to the effects of pure AChEIs. The model shows that galantamine--compared to similar concentrations of pure AChEIs--is able to compensate for its somewhat modest effect on the cholinesterase enzyme with its allosteric modulatory effects that include the additional benefit of a lower degree of receptor desensitization.

Auld et al., "Alzheimer's disease and the basal forebrain cholinergic system: relations to beta-amyloid peptides, cognition, and treatment strategies," *Prog. Neurobiol.*, 68(3):209-45 (2002) (Abstract shown below)

> Alzheimer's disease (AD) is the most common form of degenerative dementia and is characterized by progressive impairment in cognitive function during mid- to late-adult life. Brains from AD patients show several distinct neuropathological features, including extracellular beta-amyloid-containing plaques, intracellular neurofibrillary tangles composed of abnormally phosphorylated tau, and degeneration of cholinergic neurons of the basal forebrain. In this review, we will present evidence implicating involvement of the basal forebrain cholinergic system in AD pathogenesis and its accompanying cognitive deficits. We will initially discuss recent results indicating a link between cholinergic mechanisms and the pathogenic events that characterize AD, notably amyloid-beta peptides. Following this, animal models of dementia will be discussed in light of the relationship between basal forebrain cholinergic hypofunction and cognitive impairments in AD. Finally, past, present, and future treatment strategies aimed at alleviating the cognitive symptomatology of AD by improving basal forebrain cholinergic function will be addressed.

As shown by these four abstracts, nicotinic pharmacology is known to be useful in treating Alzheimer's disease. A search on MEDLINE shows hundreds of articles, in addition to the four discussed herein, showing the connection between nicotinic pharmacology and Alzheimer's disease. This showing should be sufficient to overcome any doubt the Examiner may have that nicotinic pharmacology such as that disclosed and claimed in the present application is useful for treating Alzheimer's disease.

The role of nicotinic pharmacology in treating Parkinson's disease is well known, and is established in a number of published papers, patent applications and issued patents. Abstracts from three of these papers are reproduced below.

Maggio et al., "Nicotine prevents experimental parkinsonism in rodents and induces striatal increase of neurotrophic factors," *J Neurochem* 71: 2439-2446 (1998) (Abstract shown below)

> The repeated finding of an apparent protective effect of cigarette smoking on the risk of Parkinson's disease is one of the few consistent results in the epidemiology of this disorder. Among the numerous substances that originate from tobacco smoke, nicotine is by far the most widely studied. Nicotine is a natural alkaloid that has considerable stimulatory effects on the CNS. Its effects on the CNS are mediated by the activation of neuronal heteromeric acetylcholine-gated ion channel receptors (nAChRs, also termed nicotinic acetylcholine receptors). In the present study, we describe the neuroprotective effects of (-)-nicotine in two animal models of parkinsonism: diethyldithiocarbamate-induced enhancement of 1-methyl-4-phenyl-1,2,3,6- tetrahydropyridine toxicity in mice and methamphetamine-induced neurotoxicity in rats and mice. The neuroprotective effect of (-)- nicotine was very similar to that of the noncompetitive NMDA receptor antagonist (+)-MK-801. In parallel experiments, we found that (-)- nicotine induces the basic fibroblast growth factor-2 (FGF-2) and the brain-derived neurotrophic factor in rat striatum. The effect of (-)- nicotine on the induction of FGF-2 was prevented by the nAChR antagonist mecamylamine. We also found that (+)-MK-801 was able to induce FGF-2 in the striatum. As trophic factors have been reported to be neuroprotective for dopaminergic cells, our data suggest that the increase in neurotrophic factors is a possible mechanism by which (-)- nicotine protects from experimental parkinsonisms.

Quik and Kulak, "Nicotine and nicotinic receptors: relevance to Parkinson's disease," *Neurotoxicology* 23: 581-594 (2002) (Abstract shown below)

> The development of nicotinic agonists for therapy in neurodegenerative disorders such as Parkinson's disease is an area currently receiving considerable attention. The rationale for such work stems from findings that reveal a loss of nicotinic receptors in Parkinson's disease brains. **These results, coupled with reports that nicotine treatment relieves some of the symptoms of this disorder, provides support for the contention**

that nicotine and/or nicotinic agonists may be beneficial for acute symptomatic treatment. Moreover, the observation that there is a decreased incidence of Parkinson's disease with tobacco use, possibly due to the nicotine in tobacco products, may imply that such drugs are useful for long-term neuroprotection. However, there are multiple nicotinic receptor populations in the brain with different functional properties. Identification of the subtypes involved in nigrostriatal dopaminergic activity is therefore critical for the rational use of selective therapeutic agents for symptomatic treatment and/or neuroprotection. Accumulating evidence, both in rodents and nonhuman primates now indicate that alpha6* nicotinic receptors are present on nigrostriatal dopaminergic neurons, and furthermore, that receptors containing this subunit may be most vulnerable to nigrostriatal damage, at least in nonhuman primates. These data suggest that nicotinic receptor ligands directed to alpha6* nicotinic receptors might be particularly relevant for Parkinson's disease therapeutics. (*Emphasis added*)

A more recent example is the teaching that Glial cell line-derived neurotrophic factor (GNDF) (a dopamine agonist) is useful for treating Parkinson's disease.

Grondin and Gash, "Glial cell line-derived neurotrophic factor (GDNF): a drug candidate for the treatment of Parkinson's disease," *J. Neurol.* 245(11 Suppl 3):P35-42 (1998)

Considerable effort has been devoted to the search for molecules that might exert trophic influences on midbrain dopamine neurons, and potentially be of therapeutic value in the treatment of Parkinson's disease. One such candidate is glial cell line-derived neurotrophic factor (GDNF). GNDF is distantly related to the transforming growth factor-beta superfamily and is widely expressed in many neuronal and non-neuronal tissues. GDNF uses a multisubunit receptor system in which GFRalpha-1 and Ret function as the ligand-binding and signalling components, respectively. In addition to its effects on cultured fetal midbrain dopamine neurons, GDNF promotes recovery of the injured nigrostriatal dopamine system and improves motor functions in rodent and nonhuman primate models of Parkinson's disease. Intraventricular, intrastriatal and intranigral routes of administration are efficacious in both models. In parkinsonian nonhuman primates, GDNF treatment improves bradykinesia, rigidity and postural instability. In this model,

adult midbrain dopamine neurons stimulated by GDNF show increased cell size, neuritic extent, and expression of phenotypic markers. The neurorestorative effects of a single administration of GDNF last for at least a month and can be maintained in rhesus monkeys by monthly injections. GDNF also induces neuroprotective changes in dopamine neurons, which are active within hours following trophic factor administration in rodents. The powerful neuroprotective and neurorestorative properties of GDNF seen in preclinical studies suggest that trophic factors may play an important role in treating Parkinson's disease.

Treatment of hyperkinesia is broadly within the range of disorders covered by the Vernier PCT, and also specifically taught in *J. Neural. Transm. Gen. Sect.* 96(1):9-18 (1994).

The relation between Picks' disease and nicotinic compounds is shown in at least the following papers:

Sparks et al., "Neurochemical and histopathologic alterations characteristic of Pick's disease in a non-demented individual," *J. Neuropathol. Exp. Neurol.*, 53(1):37-42 (1994) (Abstract shown below)

> In the course of investigating a large number of non-demented subjects, a 68 year old female dying of coronary artery disease was found to have Pick bodies in her grossly normal brain. Although only mild subcortical gliosis and no neuron loss were observed. Pick bodies were found throughout the brain and occasional balloon cells were noted. Pick bodies and numerous neurons were also ALZ-50 and Tau-1 immunoreactive. Retrospective studies indicated a lack of overt intellectual decline or depression in this individual. Frontal, temporal and occipital poles, amygdala, hypothalamus and nucleus basalis of Meynert (nbM) were analyzed for ChAT, AChE and MAO-A and -B enzymatic activities and for the binding of 5HT and imipramine. Cholinergic decreases were found only in subcortical structures. Serotonin binding decreases were widespread, excluding the nbM. Altered MAO-B activity was regionally variable, and no differences in MAO-A activity or imipramine binding were observed. Few differences in neurochemical alterations were observed in the current non-demented subject with abundant Pick bodies compared to previous studies of demented Pick's patients. This case strongly suggests that

chemical dysfunction and neuropathological features of Pick's disease occur in advance of overt clinical manifestations of the disorder.

Yates et al., "Neurochemical observations in a case of Pick's disease," *J. Neurol. Sci.*, **48(2)**:257-63 (1980) (Abstract shown below):

> Neurochemical markers of the activities of the cholinergic, gabaergic and dopaminergic systems were measured in post-mortem brain from a case of Pick's disease. No marked changes were found in the activities of choline acetyltransferase, acetylcholinesterase, L-glutamic acid decarboxylase and the concentration of dopamine. In areas of brain showing no histological changes, muscarinic receptor binding was within the normal range. In the cerebral cortex, which exhibited the neuropathological features of Pick's disease, the number of muscarinic cholinergic binding sites was much reduced, suggesting that the cortical neurones which are lost in Pick's disease are cholinoceptive.

Kanazawa et al., "Studies on neurotransmitter markers of the basal ganglia in Pick's disease, with special reference to dopamine reduction," *J. Neurol. Sci.* **83(1)**:63-74 (1988) (Abstract shown below)

> gamma-Aminobutyric acid (GABA), substance P and dopamine concentrations and choline acetyltransferase (ChAT) activity were measured in post-mortem cerebrocortical and basal ganglial areas of 14 controls and 4 patients with pathologically verified Pick's disease (1 classic case and 3 cases of the generalized form). GABA and substance P levels in the substantia nigra and the globus pallidus were generally decreased, corresponding to the moderate to severe loss of small neurones in the striatum. ChAT activities in the striatum varied from case to case, in proportion to various degrees of loss of large neurones in the striatum. These neurotransmitter abnormalities in Pick's disease were exactly the same as those in Huntington's disease. However, dopamine concentrations were markedly reduced in the striatum in Pick's disease, whereas striatal dopamine in Huntington's disease is reported to be increased. A dopamine reduction in

the striatum of Pick's disease was more disproportionately prominent than expected for various degrees of nigral cell loss. This may be one of the important factors which prevents the generation of choreic movements in Pick's disease in spite of definite striatal atrophy similar to Huntington's disease.

Guard et al., "Cerebral metabolism of dopamine and of serotonin during Alzheimer and Pick's diseases. Dynamic study by the test using probenecid," *Encephale* 2(4):293-303 (1976)

[Article in French, Abstract shown below]

A study of the cerebral metabolism of dopamine and serotonin has been realized by the probenecid test in 17 patients. The diagnosis of Alzheimer's disease (13 patients) and Pick's disease (4 patients) has been made on clinical and radiological grounds. No important anomaly of this metabolism was discovered. In subjects with Alzheimer's disease, the renewal rates of H.V.A. and 5 H.I.A.A. were diminished in comparison to the values measured in normal individuals, but this difference was not significant. In patients with Pick's disease, the accumulation of H.V.A. after probenecid was in the normal bounds, whereas that of 5 H.I.A.A. was non-significantly decreased. The results are compared with those of the literature.

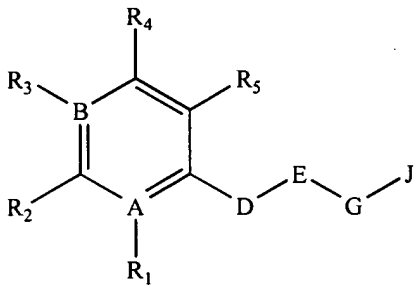
PCT Applications WO 03/22856, 03/18585 and 03/18586 also teach the use of nicotinic compounds (though not the nicotinic compounds as presently claimed) to treat Pick's disease.

Accordingly, Applicants believe they have provided adequate literature support for the proposition that nicotinic pharmacology is useful for treating each of the listed indications. In light of the amendments, comments and literature citations presented herein, the Examiner is respectfully requested to withdraw the enablement rejections.

Rejections under 35 U.S.C. 103(a)

Claims 1-16, 22-41, 48-66 and 73-75 have been rejected under 35 U.S.C. 103(a), first paragraph, as obvious in view of PCT WO 99/32117 to Vernier ("Vernier"). Applicants respectfully traverse the rejections if applied to the amended claims.

Vernier teaches compounds of the following formula:



where A and B can independently be C or N, with the proviso that at least one of A and B is N. R_{1-5} can be any of a variety of substituents. D is optional, and can be alkyl, cycloalkyl, alkylene or alkynylene. E is optional, and is selected from –O-, -CO-, -CONRc-, -C(O)O-, -OC(O)NRc-, -S-, -S(O)-, -S(O)NRc-, $-S(O)_2-$, $-S(O)_2NRc-$ or -S(O)=NH, where Rc is hydrogen, lower alkyl or substituted lower alkyl. G is optional, and can be alkylene, substituted alkylene, alkenylene or substituted alkenylene. J is a dialkylamino (including various cyclic and bicyclic amino groups). Since J is dialkylamino, if E is present, G must also be present or J cannot be dialkylamino. It is preferred that D is either not present or is lower alkylene (page 16, lines 19-23).

The compounds described in Vernier each have a side chain that is one or three positions removed from a ring nitrogen (either A or B). Vernier does not teach or suggest compounds where the side chain is attached two positions removed from a ring nitrogen, as required by the claims. The obviousness rejection should be withdrawn on this basis alone.

For the compounds in Vernier to even be positional isomers of the claimed compounds, it would require a non-obvious selection of various values for substituents D, E, G and J.
Of all of the listed substituents, D would have to be alkenylene, E would have to be absent, G would have to be alkylene, and J would not only have to be dialkylamino, but would have to be the specific monocyclic and bicyclic compounds (Q) in the instant claims. Absent impermissible hindsight, this would be involve a non-obvious selection from a myriad of possibilities, including

alkyl and alkynyl substitutions at both D and G, numerous heteroatom-substituted moieties at E, and numerous acyclic amines at J.

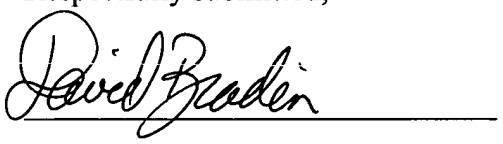
The claims were limited to the situation where the only ring nitrogen was at the position two carbons from the side chain in response to a Restriction Requirement mailed in connection with the above-identified application on February 13, 2002. The Restriction Requirement stated that the claims included four separate inventions, in Groups I-IV, where X' and X are nitrogen, X' is nitrogen and X is carbon, X' is carbon and X is nitrogen, and X' and X are carbon. The Examiner's stated position was that these compounds were independent and distinct from one another because they are dissimilar compounds with varying cores, the groups have different classifications and require separate prior art searches, and art relevant to one group of compounds may not be relevant to another group of compounds.

The Examiner now states that it would be an obvious variation to move the position of the nitrogen atom in the ring relative to the side chain. The Examiner's position in the present action is inconsistent with that taken in the Restriction Requirement, and the obviousness rejection should accordingly be withdrawn.

It is believed that the above-mentioned amendments and comments address each of the rejections. In light of the above-mentioned amendments and comments, Applicants respectfully request prompt issuance of a Notice of Allowance. The Examiner is invited to Applicants' undersigned representative at the telephone number below should any issues remain.

Respectfully submitted,

Date: April 7, 2003



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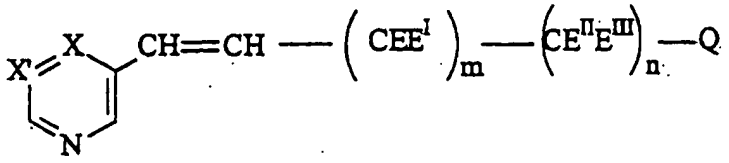
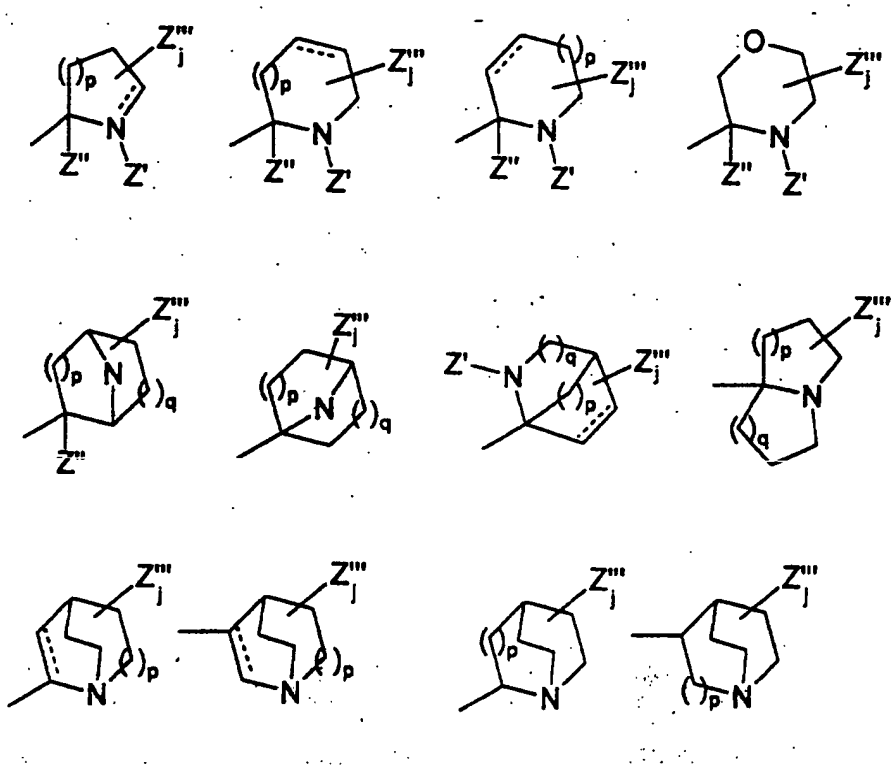
APPENDIX - AMENDED CLAIMS

1. (Three Times Amended) A compound of the formula:



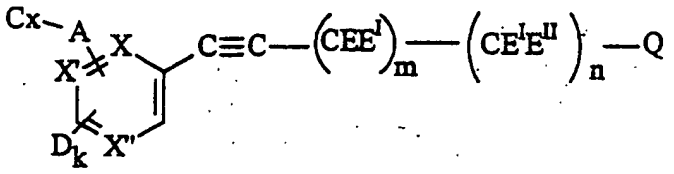
where X and X' are individually carbon bonded to a substituent species selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, heterocyclyl, substituted heterocyclyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl; arylalkyl, substituted arylalkyl, halo, -OR', -NR'R", $-CF_3$, -CN, $-NO_2$, $-C_2R'$, -SR', $-N_3$, C(=O)NR'R", -NR'C(=O)R", -C(=O)R', -C(=O)OR', -OC(=O)R', $-O(CR'R")_rC(=O)R'$, $-O(CR'R")_rNR'R"$ $-O(CR'R")_rNR"C(=O)R'$, $-O(CR'R")_rNR"SO_2R'$, -OC(=O)NR'R", -NR'C(=O)O R", $-SO_2R'$, $-SO_2NR'R"$, and $-NR'SO_2R"$, where R' and R" are individually hydrogen, lower alkyl, cycloalkyl, heterocyclyl, or an aromatic group-containing species selected from the group consisting of phenyl, benzyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, indolyl and quinolinyl, and r is an integer from 1 to 6, or R' and R" can together form a cycloalkyl group; m is an integer and n is an integer such that the sum of m plus n is 0, 1, 2 or 3; E, E^I, E^{II} and E^{III} individually represent hydrogen or a suitable non-hydrogen substituent selected from the group consisting of alkyl, substituted alkyl, halo-substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, arylalkyl and substituted arylalkyl; and Q is selected from:



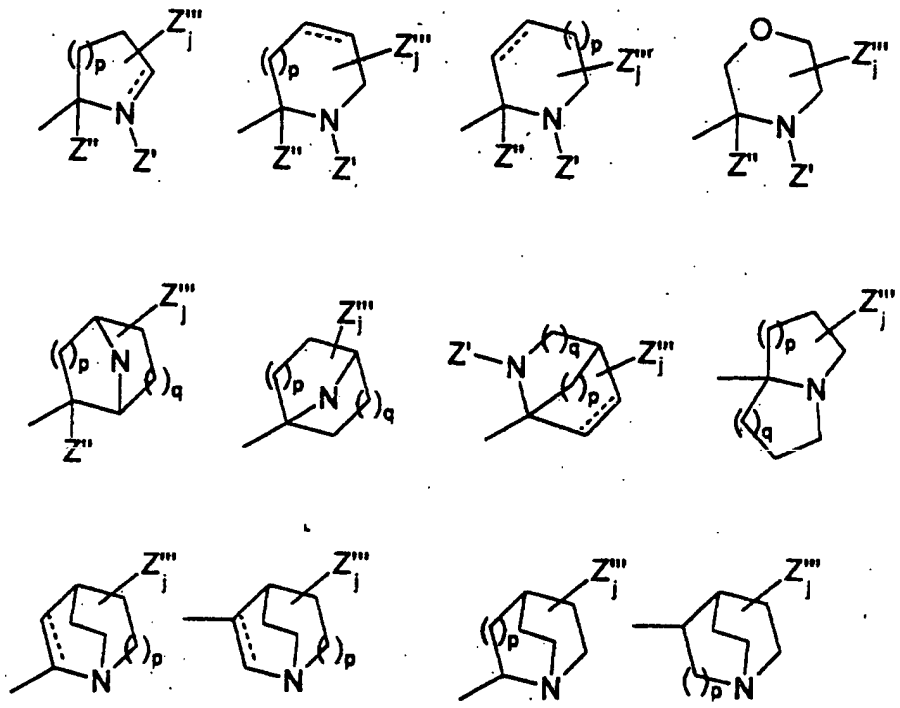
where Z' represents hydrogen or lower alkyl, acyl, alkoxycarbonyl, or aryloxycarbonyl; Z" is hydrogen or lower alkyl; and Z''' is a non-hydrogen substituent selected from the group consisting of alkyl, substituted alkyl, halo-substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, arylalkyl and substituted arylalkyl; the dotted line indicates a carbon-carbon single bond or a carbon-carbon double bond, p is 0, 1 or 2; q is 0, 1, 2 or 3; and j is an integer from 0 to 3,

wherein Z'''j refers to j number of Z''' substituents.

16. (Three Times Amended) A compound of the formula:



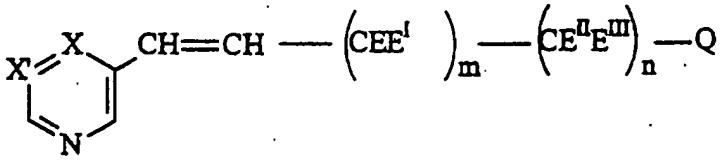
where X" is nitrogen and X, X' are individually carbon bonded to a substituent species selected from the group consisting of hydrogen alkyl, substituted alkyl, alkenyl, substituted alkenyl, heterocyclyl, substituted heterocyclyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl; arylalkyl, substituted arylalkyl, halo, -OR', -NR'R", $-CF_3$, -CN, $-NO_2$, $-C_2R'$, -SR', $-N_3$, C(=O)NR'R", -NR'C(=O)R", -C(=O)R', -C(=O)OR', -OC(=O)R', $-O(CR'R")_rC(=O)R'$, $-O(CR'R")_rNR'R"$ $-O(CR'R")_rNR"C(=O)R'$, $-O(CR'R")_rNR"SO_2R'$, -OC(=O)NR'R", -NR'C(=O)O R", $-SO_2R'$, $-SO_2NR'R"$, and $-NR'SO_2R"$, where R' and R" are individually hydrogen, lower alkyl, cycloalkyl, heterocyclyl, or an aromatic group-containing species selected from the group consisting of phenyl, benzyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, indolyl and quinolinyl, and r is an integer from 1 to 6, or R' and R" can together form a cycloalkyl group; A is O, C=O or a covalent bond; D is a suitable non-hydrogen substituent species selected from the group of substituent species for X, X' and X"; k is 0, 1 or 2; Cx is selected from a group consisting of aryl, substituted aryl, heteroaryl, substituted heteroaryl, non-aromatic heterocyclyl, substituted non-aromatic heterocyclyl, non-aromatic heterocyclylalkyl and substituted non-aromatic heterocyclylalkyl; m is an integer and n is an integer such that the sum of m plus n is 0, 1, 2 or 3; E, E^I, E^{II} and E^{III} individually represent hydrogen or a suitable non-hydrogen substituent selected from the group consisting of alkyl, substituted alkyl, halo-substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, arylalkyl and substituted arylalkyl; and Q is selected from:



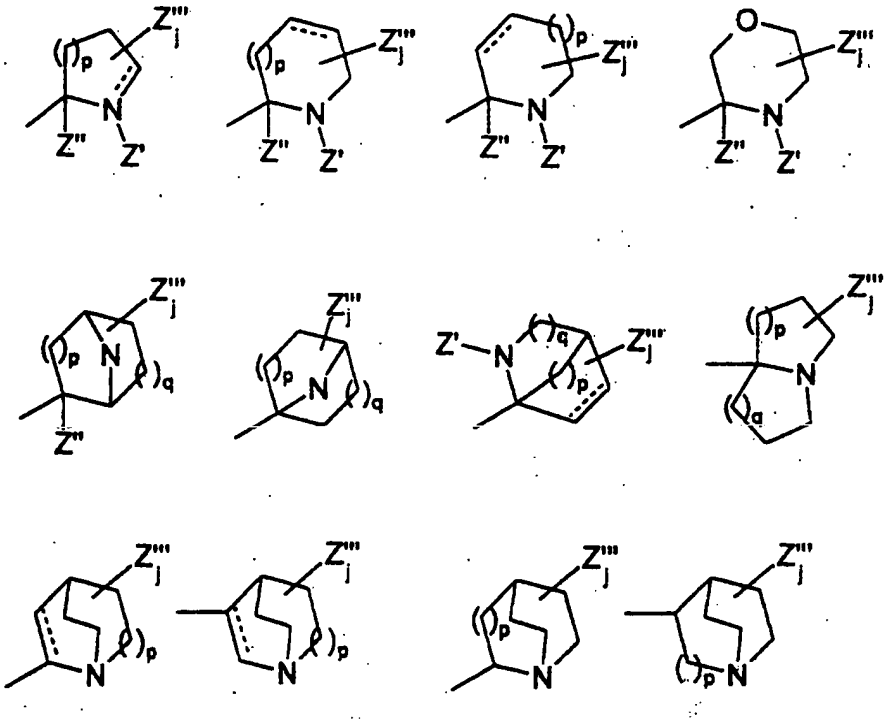
where Z' represents hydrogen or lower alkyl, acyl, alkoxycarbonyl, or aryloxycarbonyl; Z" is hydrogen or lower alkyl; and Z"' is a non-hydrogen substituent selected from the group consisting of alkyl, substituted alkyl, halo-substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, arylalkyl and substituted arylalkyl; the dotted line indicates a carbon-carbon single bond or a carbon-carbon double bond; p is 0, 1 or 2; q is 0, 1, 2 or 3; and j is an integer from 0 to 3,

wherein Z'"j refers to j number of Z"' substituents.

25. (Three Times Amended) A pharmaceutical composition incorporating a compound of



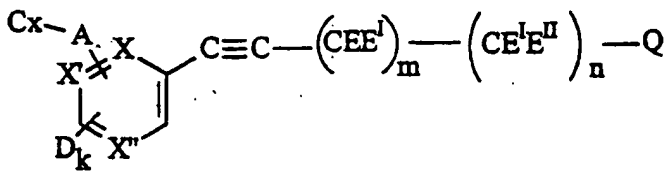
where X and X' are individually carbon bonded to a substituent species selected from the group consisting of hydrogen alkyl, substituted alkyl, alkenyl, substituted alkenyl, heterocyclyl, substituted heterocyclyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl; arylalkyl, substituted arylalkyl, halo, -OR', -NR'R", $-CF_3$, -CN, $-NO_2$, $-C_2R'$, -SR', $-N_3$, C(=O)NR'R", -NR'C(=O)R", -C(=O)R', -C(=O)OR', -OC(=O)R', $-O(CR'R")_rC(=O)R'$, $-O(CR'R")_rNR'R"$ $-O(CR'R")_rNR"C(=O)R'$, $-O(CR'R")_rNR"SO_2R'$, -OC(=O)NR'R", -NR'C(=O)O R", $-SO_2R'$, $-SO_2NR'R"$, and $-NR'SO_2R"$, where R' and R" are individually hydrogen, lower alkyl, cycloalkyl, heterocyclyl, or an aromatic group-containing species selected from the group consisting of phenyl, benzyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, indolyl and quinolinyl, and r is an integer from 1 to 6, or R' and R" can together form a cycloalkyl group; m is an integer and n is an integer such that the sum of m plus n is 0, 1, 2 or 3; E, E^I, E^{II} and E^{III} individually represent hydrogen or a suitable non-hydrogen substituent selected from the group consisting of alkyl, substituted alkyl, halo-substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, arylalkyl and substituted arylalkyl; and Q is selected from:



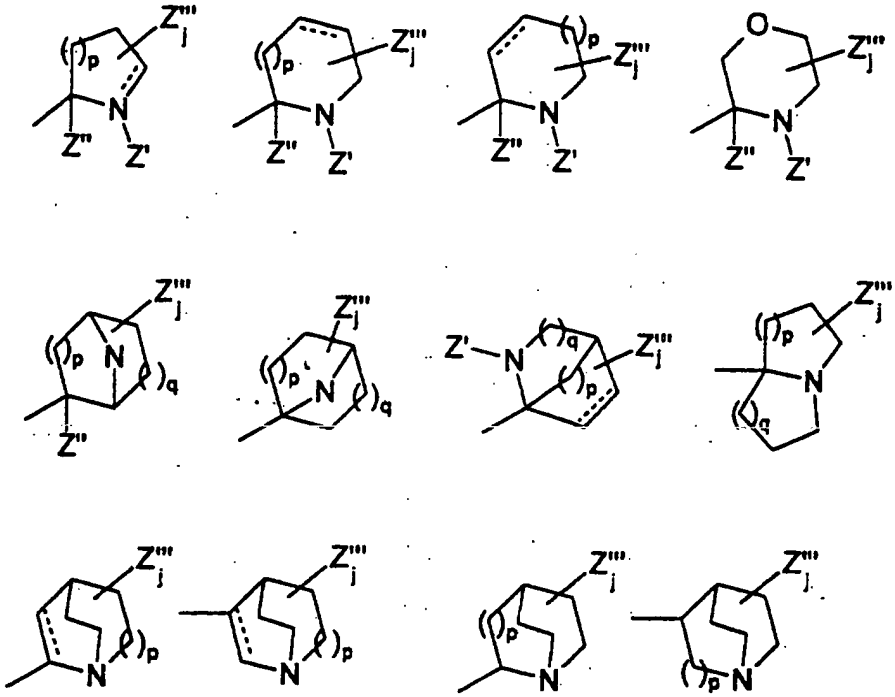
where Z' represents hydrogen or lower alkyl, acyl, alkoxycarbonyl, or aryloxycarbonyl; Z" is hydrogen or lower alkyl; and Z"' is a non-hydrogen substituent selected from the group consisting of alkyl, substituted alkyl, halo-substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, arylalkyl and substituted arylalkyl; the dotted line indicates a carbon-carbon single bond or a carbon-carbon double bond; p is 0, 1 or 2; q is 0, 1, 2 or 3; and j is an integer from 0 to 3, along with a pharmaceutically acceptable carrier,

wherein Z'"j refers to j number of Z'" substituents.

41. (Three Times Amended) A pharmaceutical composition incorporating a compound of the formula:



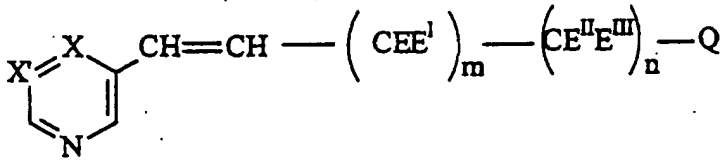
where X" is nitrogen and X and X' are individually carbon bonded to a substituent species selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, heterocyclyl, substituted heterocyclyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl; arylalkyl, substituted arylalkyl, halo, -OR', -NR'R", -CF_3, -CN, -NO_2, -C_2R', -SR', -N_3, C(=O)NR'R", -NR'C(=O)R", -C(=O)R', -C(=O)OR', -OC(=O)R', -O(CR'R")$_r$C(=O)R', -O(CR'R")$_r$NR'R" -O(CR'R")$_r$NR"C(=O)R', -O(CR'R")$_r$NR"SO_2R', -OC(=O)NR'R", -NR'C(=O)O R", -SO_2R', -SO_2NR'R", and -NR'SO_2R", where R' and R" are individually hydrogen, lower alkyl, cycloalkyl, heterocyclyl, or an aromatic group-containing species selected from the group consisting of phenyl, benzyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, indolyl and quinolinyl, and r is an integer from 1 to 6, or R' and R" can together form a cycloalkyl group; A is O, C=O or a covalent bond; D is a suitable non-hydrogen substituent species selected from the group of substituent species for X, X' and X"; k is 0, 1 or 2; Cx is selected from a group consisting of aryl, substituted aryl, heteroaryl, substituted heteroaryl, non-aromatic heterocyclyl, substituted non-aromatic heterocyclyl, non-aromatic heterocyclylalkyl and substituted non-aromatic hetero-cyclylalkyl; m is an integer and n is an integer such that the sum of m plus n is 0, 1, 2 or 3; E, E^I, E^{II} and E^{III} individually represent hydrogen or a suitable non-hydrogen substituent selected from the group consisting of alkyl, substituted alkyl, halo-substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, arylalkyl and substituted arylalkyl; and Q is selected from:



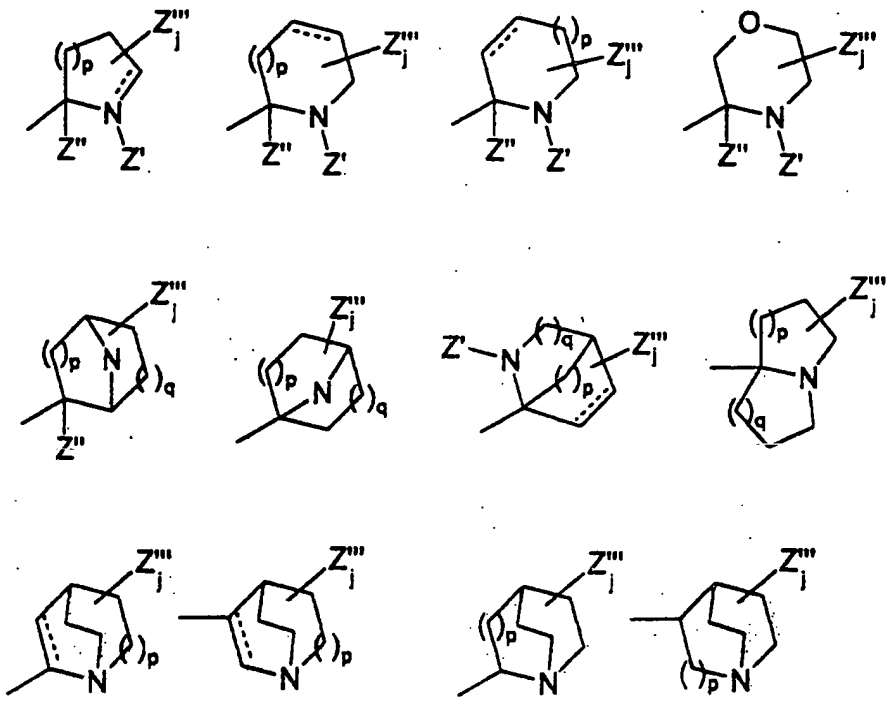
where Z' represents hydrogen or lower alkyl, acyl, alkoxycarbonyl, or aryloxycarbonyl; Z" is hydrogen or lower alkyl; arid Z"' is a non-hydrogen substituent selected from the group consisting of alkyl, substituted alkyl, halo-substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, arylalkyl and substituted arylalkyl; the dotted line indicates a carbon-carbon single bond or a carbon-carbon double bond; p is 0, 1 or 2; q is 0, 1, 2 or 3; and j is an integer from 0 to 3, and a pharmaceutically acceptable carrier,

wherein Z'"j refers to j number of Z'" substituents.

51. (Three Times Amended) A method for treating a central nervous system disorder associated with dysfunction of nicotinic receptors, said method comprising administering an effective amount of a compound having the formula:



where X and X' are individually carbon bonded to a substituent species selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, heterocyclyl, substituted heterocyclyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl; arylalkyl, substituted arylalkyl, halo, -OR', -NR'R", $-CF_3$, -CN, $-NO_2$, $-C_2R'$, -SR', $-N_3$, C(=O)NR'R", -NR'C(=O)R", -C(=O)R', -C(=O)OR', -OC(=O)R', $-O(CR'R")_rC(=O)R'$, $-O(CR'R")_rNR'R"$ $-O(CR'R")_rNR"C(=O)R'$, $-O(CR'R")_rNR"SO_2R'$, -OC(=O)NR'R", -NR'C(=O)O R", $-SO_2R'$, $-SO_2NR'R"$, and $-NR'SO_2R"$, where R' and R" are individually hydrogen, lower alkyl, cycloalkyl, heterocyclyl, or an aromatic group-containing species selected from the group consisting of phenyl, benzyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, indolyl and quinolinyl, and r is an integer from 1 to 6, or R' and R" can together form a cycloalkyl group; m is an integer and n is an integer such that the sum of m plus n is 0, 1, 2 or 3; E, E^I, E^{II} and E^{III} individually represent hydrogen or a suitable non-hydrogen substituent selected from the group consisting of alkyl, substituted alkyl, halo-substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, arylalkyl and substituted arylalkyl; and Q is selected from:

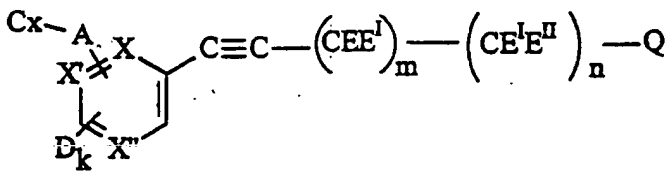


where Z' is hydrogen, lower alkyl, acyl, alkoxycarbonyl, or aryloxycarbonyl; Z" is hydrogen or lower alkyl; and Z"' is a non-hydrogen substituent selected from the group consisting of alkyl, substituted alkyl, halo-substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, arylalkyl and substituted arylalkyl; the dotted line indicates a carbon-carbon single bond or a carbon-carbon double bond; p is 0, 1 or 2; q is 0, 1, 2 or 3; and j is an integer from 0 to 3,

wherein Z'"j refers to j number of Z'" substituents, and

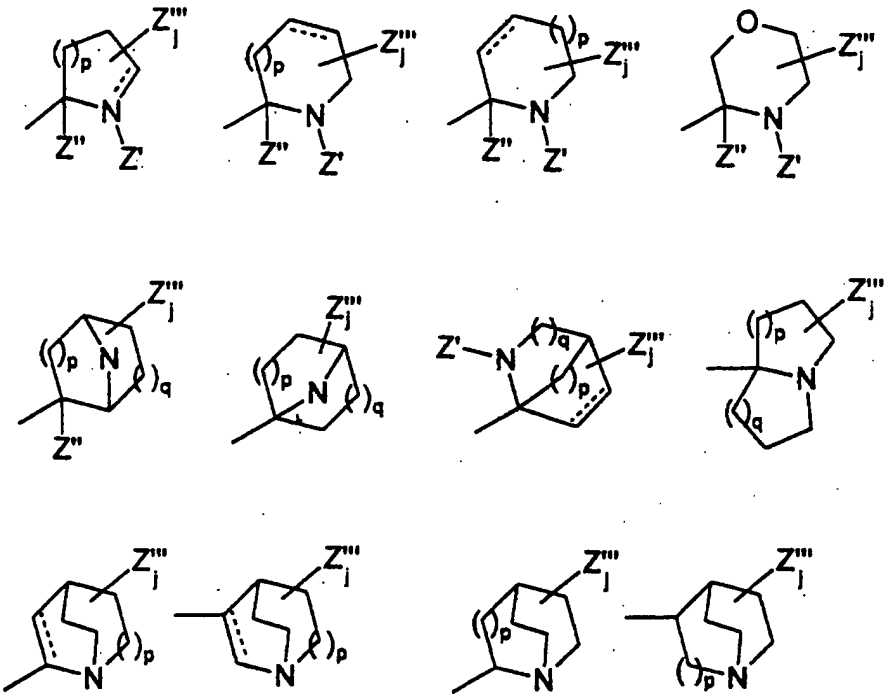
wherein the central nervous system disorder is selected from the group consisting of pre-senile dementia, senile dementia, HIV-dementia, multiple cerebral infarcts, Parkinsonism, Pick's disease, Huntington's chorea, tardive dyskindesia, hyperkinesias, mania, attention deficit disorder, anxiety, depression, mild cognitive impairment, dyslexia, schizophrenia and Tourette's syndrome.

66. (Three Times Amended) A method for treating a central nervous system disorder associated with dysfunction of nicotinic receptors, said method comprising of the administration of an effective amount of a compound having the formula:



where X" is nitrogen, X and X' are individually carbon bonded to a substituent species selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, heterocyclyl, substituted heterocyclyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl; arylalkyl, substituted arylalkyl, halo, -OR', -NR'R", $-CF_3$, -CN, $-NO_2$, $-C_2R'$, -SR', $-N_3$, C(=O)NR'R", -NR'C(=O)R", -C(=O)R', -C(=O)OR', -OC(=O)R', $-O(CR'R")_rC(=O)R'$, $-O(CR'R")_rNR'R"$ $-O(CR'R")_rNR"C(=O)R'$, $-O(CR'R")_rNR"SO_2R'$, -OC(=O)NR'R", -NR'C(=O)O R", $-SO_2R'$, $-SO_2NR'R"$, and $-NR'SO_2R"$, where R' and R" are individually hydrogen, lower alkyl, cycloalkyl, heterocyclyl, or an aromatic group-containing species selected from the group consisting of phenyl, benzyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, indolyl and quinolinyl, and r is an integer from 1 to 6, or R' and R" can together form a cycloalkyl group; A is O, C=O or a covalent bond; D is a suitable non-hydrogen substituent species selected from the group of substituent species for X, X' and X"; k is 0, 1 or 2; Cx is selected from a group consisting of aryl, substituted aryl, heteroaryl, substituted heteroaryl, non-aromatic heterocyclyl, substituted non-aromatic heterocyclyl, non-aromatic heterocyclylalkyl and substituted non-aromatic hetero-cyclylalkyl; m is an integer and n is an integer such that the sum of m plus n is 0, 1, 2 or 3; E, E^I, E^{II} and E^{III} individually represent hydrogen or a suitable non-hydrogen substituent selected from the group consisting of alkyl, substituted alkyl, halo-substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl,

substituted aryl, alkylaryl, substituted alkylaryl, arylalkyl and substituted arylalkyl; and Q is selected from:



where Z' is hydrogen, lower alkyl, acyl, alkoxycarbonyl, or aryloxycarbonyl; Z" is hydrogen or lower alkyl; and Z"' is a non-hydrogen substituent selected from the group consisting of alkyl, substituted alkyl, halo-substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, arylalkyl and substituted arylalkyl; the dotted line indicates a carbon-carbon single bond or a carbon-carbon double bond; p is 0, 1 or 2; q is 0, 1, 2 or 3; and j is an integer from 0 to 3,

wherein Z"'j refers to j number of Z"' substituents, and

wherein the central nervous system disorder is selected from the group consisting of pre-senile dementia, senile dementia, HIV-dementia, multiple cerebral infarcts, Parkinsonism, Pick's disease, Huntington's chorea, tardive dyskindesia, hyperkinesias, mania, attention deficit

disorder, anxiety, depression, mild cognitive impairment, dyslexia, schizophrenia and Tourette's syndrome.